

## Molecular Dynamics II

### 3070-Pos Board B762

#### Development of an All-Atom/Coarse Grain, Mixed Resolution Model for Proteins and their Environment

Jianing Li<sup>1</sup>, Amanda Jonsson<sup>2</sup>, Sven Jakobtorweihen<sup>3</sup>, Mee Y. Shelley<sup>4</sup>, Gregory A. Voth<sup>1</sup>, Ramy Farid<sup>5</sup>, John C. Shelley<sup>4</sup>.

<sup>1</sup>University of Chicago, Chicago, IL, USA, <sup>2</sup>The University of Wisconsin - Stevens Point, Stevens Point, WI, USA, <sup>3</sup>Hamburg University of Technology, Hamburg, Germany, <sup>4</sup>Schrodinger, Inc., Portland, OR, USA, <sup>5</sup>Schrodinger, Inc., New York, NY, USA.

Coarse graining usually results in significantly faster simulations at the cost of reducing accuracy relative to atomistic representations. One must choose what to coarse grain carefully. Atomistic simulations of proteins, particularly to study conformational changes of proteins, are of great interest but hard to propagate long enough to obtain sufficient sampling. Protein and drug-molecule interactions and conformational behavior are quite intricate, significantly limiting applications from simplified models such as coarse grain approaches. However, water and membrane lipids are readily amenable to coarse graining suggesting that an approach in which the protein and ligand retain atomistic representations while their environment is simplified. As an experiment, we have developed such a mixed resolution model and have applied it to a GPCR, globular proteins and antimicrobial peptides. We present those results to highlight what is working well and what challenges remain for this approach.

### 3071-Pos Board B763

#### Identifying Local Regions of Order and Disorder in FG-Nucleoporins and Partially Disordered Proteins Using Molecular Dynamics Simulations

Timothy G. Connolly<sup>1</sup>, David Ando<sup>1</sup>, Robert L. Wang<sup>2</sup>, Ajay Gopinathan<sup>1</sup>, Shawn D. Newsam<sup>1</sup>, Michael E. Colvin<sup>1</sup>.

<sup>1</sup>School of Natural Sciences, University of California, Merced, Merced, CA, USA, <sup>2</sup>School of Engineering, University of California, Merced, Merced, CA, USA.

Analysis tools optimized to study molecular dynamics (MD) simulations of intrinsically disordered proteins (IDPs) are currently rare. We are developing a set of tools using the libraries and interface of the widely used MD simulation software Gromacs 4 [Hess, et al. 2008]. We are presenting the results of one of these tools which shows utility in differentiating between ordered and disordered regions of proteins based on MD simulation trajectories. This tool assigns a value along a spectrum of order to disorder to a protein based on a scaled average of all inter-structure distances and is based on a previously proposed and intuitive algorithm [Stultz, et al. 2011]. The primary improvements made to this algorithm include additional options of inter-structure distance metrics, a feature to assign values of disorder to individual amino acids, and an output format similar to currently available disorder prediction tools which use amino acid sequence information. When applied to systems of highly disordered protein, this tool is sometimes able to differentiate the regions of secondary structure formed during MD simulations. We are currently studying applications to partially disordered proteins to simplify the identification of local ordered and disordered regions from MD simulation trajectories. This method also provides multiple options of inter-structure distance metrics to optimize the analysis of both mostly ordered and highly flexible proteins. We are validating this usage of the tool with (1) a coarse grain model of several FG-nucleoporin sequences believed to be IDPs with varying levels of disorder spread across different regions and (2) all atom simulations of partially disordered proteins including a fragment of the tumor suppressor protein p53.

### 3072-Pos Board B764

#### How Structural Fluctuations of the ATP Pocket Influence the Catalytic Cycle of FAK

Florian Herzog, Vogel Viola.

Department Health Science and Technology, ETH Zurich, Zurich, Switzerland.

The focal adhesion kinase (FAK) is a key regulator of cell shape, adhesion and migration. While the structure of the active and the inhibited kinase domain is known, little is known about the dynamic processes regulating the catalytic cycle. Here, we investigate the dynamics of the active and inactive conformation of the kinase domain of FAK upon removal of ligands.

Using molecular dynamics simulations, we show that the nucleotide-binding pocket in the catalytically active conformation is structurally unstable and fluctuates between an open and closed configuration upon removal of the ATP-analog. Several hydrogen bonds can form between the upper and lower lobes of the pocket. In contrast, the pocket remains open in the catalytically inactive form without ligand. The average distance between the pocket forming residues is lower and more hydrogen bonds are formed in the active compared to the inactive kinase.

The simulations suggest a multi-step process in which the kinase is more likely to bind ATP in the inactive than in the active form. The transient closures of the ATP pocket might allow FAK to slow down its catalytic cycle, and to adapt its kinetics to the crowded environments of focal adhesions.

### 3073-Pos Board B765

#### Molecular Dynamics Simulations of Laser-Induced and pH-Induced Unfolding in $\beta$ -Lactoglobulin at Different Hydration Levels

James E. Parker<sup>1</sup>, Aaron F. Hoffman<sup>2</sup>, Robert J. Thomas<sup>3</sup>, Lorenzo Brancaloni<sup>1</sup>.

<sup>1</sup>Department of Physics and Astronomy, The University of Texas at San Antonio, San Antonio, TX, USA, <sup>2</sup>Department of Physics, Fort Hays State University, Hays, KS, USA, <sup>3</sup>Optical Radiation Bioeffects Branch, Bioeffects Division, Human Effectiveness Directorate, 711th Human Performance Wing, Air Force Research Laboratory, JBSA Fort Sam Houston, TX, USA. Computational molecular dynamics simulations were used to estimate the unfolding effects of a single electron positioned appropriately in a globular protein of interest,  $\beta$ -lactoglobulin (BLG). Two sets of unfolding simulations were conducted: movement of the EF-loop in BLG, which is involved in the Tanford transition and a photo-induced electron transfer event between a non-covalently bound, dye molecule, meso-tetrakis p-sulfonatophenyl porphyrin, (TSPP) and BLG.

The first simulations solvated BLG at several hydration levels for two different crystal structures: 3BLG at pH 7 (closed loop) and 2BLG at pH 9 (open loop), which became the reference initial and final structures to determine the accuracy of our simulations. Movement of the EF-loop was induced by placing an excess charge on the carboxyl group of glutamic acid residue GLU 89. After 10 ns, favorable structures were submitted to a residue based, coarse-graining algorithm to enable simulating 0.1 ms of the loop motion. The goal was three-fold: to allow the crystallized form to relax in an aqueous environment, to determine the minimal number of explicit water molecules that are sufficient to retain the thermodynamics of the system, and to verify the charge placement algorithm. For the second phase, the location of the electron transfer event was determined by the most probable binding site of the ligand that correlated with resonance Raman spectra and docking calculations of the TSPP-BLG complex. Residues within 3 Å were examined for alignment with the ligand and electron affinity. Candidate sites became the origin of an excess electron on the protein, and a separate computation was conducted with coarse-graining methods applied to favorable trajectories as described above. The unfolding determined by these simulations was compared to previously collected circular dichroism data of TSPP-BLG complexes.

### 3074-Pos Board B766

#### In Silico Dynamics of Carbon Monoxide in the Active Site Pocket of Nitrogenase

Leland B. Gee<sup>1</sup>, Igor Leontyev<sup>2</sup>, Stephen P. Cramer<sup>2</sup>.

<sup>1</sup>Biophysics, University of California, Davis, Davis, CA, USA, <sup>2</sup>Chemistry, University of California, Davis, Davis, CA, USA.

The Nitrogenase enzyme system catalyzes the reduction of dinitrogen ( $N_2$ ) to, the more biologically utilizable, ammonia at the site of an unusual  $[Fe_7S_9MoC]$  cofactor named "FeMo-co". The mechanism of enzymatic nitrogen fixation remains a mystery due to the transient nature of the reaction intermediates, and many investigators have sought to look at the reversible inhibitor carbon monoxide (CO) as an analogue to the dynamics and kinetics of the natural substrate. Previous work has proposed that a  $\mu^2$ -CO can bind to the Fe-2 and Fe-6 of a 4Fe-4S ( $Fe-[2,3,6,7]$ ) face of FeMo-co, and dependent on binding conditions, as a terminal ligand. We investigated the ligand-active site dynamics around FeMo-co for CO using the molecular dynamics package GROMACS, for both wild type and key residue mutants. The purpose of investigation was to determine: if the Fe-2 or Fe-6 served as a more sterically accessible binding site for terminal CO, the location of any active site pockets to trap CO near FeMo-co, and to probe the dynamics of the proximal gas channel entrance to the active site. The results of this research can be used to improve the existing model for reversible CO inhibition dynamics of Nitrogenase. Furthermore, these data will lead to new kinetics experiments involving CO and *in vitro* active site mutagenesis. Finally, our conclusions can be abstracted to provide clues about the short-lived active site behavior of the substrate  $N_2$ .

### 3075-Pos Board B767

#### Studying the Effects of Methionine Oxidation on Human Fibrin with Multiscale Simulations

Patrick R. Burney, Jim Pfaendtner.

Chemical Engineering, University of Washington, Seattle, WA, USA.

Oxidation of key methionine residues on fibrin leads to reduced lateral aggregation in fibrin gels and prolonged fibrinolysis by tissue plasminogen activator. These observations may reveal the mechanism by which the detrimental